UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912

23379 7590 07/15/2008

RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMENTE, CA 92672

EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
07/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

RICHARD@SCI-TECH.COM
jan@sci-tech.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEVIN H. GARDNER, CARLOS A. AMEZCUA, PAULUS J.A. ERBEL, PAUL B. CARD, SHANNON HARPER, JARED RUTTER, RICHARD K. BRUICK, STEVEN L. MCKNIGHT

Appeal 2008-2542
Application 10/677,734
Technology Center 1600

Decided: July 11, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claim 21. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Claim 21 is directed to a method of changing the surface binding specificity of the HIF2a PAS B domain. HIF2a is a hypoxia inducible factor (HIF) "that mediates responses to lowered oxygen levels in mammalian cells" (Spec. 17: 19-20). It contains a PAS (Per-ARNT-Sim) B domain which is a protein interaction domain widely used for intra- and intermolecular associations (Spec. 1: 17-18).

Claims 21 and 22 are pending; claim 22 is withdrawn from consideration. Claim 21 stands finally rejected as follows:

1) under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement (Ans. 3);

2) under 35 U.S.C. § 112, first paragraph for lack of written description (Ans. 5); and

2) under 35 U.S.C. § 103(a) as obvious over Vogtherr ("NMR-based screening method for lead discovery," *Modern Methods of Drug Discovery,* 93: 183-202, 2003) or Amezcua ("Structure and Interactions of PAS Kinase N-Terminal PAS Domain: Model for Intramolecular Kinase Regulation," *Structure*, 10: 1349-1361, 2002) in view of Ema ("A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1α regulates the VEGF expression and is potentially involved in lung and vascular development," *Proc. Natl. Acad. Sci. USA,* 94: 4273-4278, 1997) and Fukunaga ("Identification of Functional Domains of the Aryl Hydrocarbon Receptor," *The Journal of Biological Chemistry,* 270(49): 29270-29278, 1995) (Ans. 6).

Claim 21 reads:

> A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:
>
> introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and
>
> detecting a resultant change in the functional surface binding specificity of the PAS domain,
>
> wherein the PAS domain is HIF2a PAS B, and the binding specificity is an intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by 1H/15N-HSQC NMR, wherein PAS refers to Per-ARNT-Sim, ARNT refers to acyl hydrocarbon receptor nuclear translocator, and HIF2a refers to hypoxia inducible factor 2 alpha.

DISCUSSION

Claim 21 is directed to a method of "changing a functional surface binding specificity" of the "HIF2a PAS B domain." The method comprises two steps: 1) introducing a ligand into the hydrophobic core of the PAS B domain; and 2) "detecting resultant change in the functional surface binding specificity of the PAS domain." The change in binding specificity is "detected as a change in chemical shifts detected by 1H/15N-HSQC NMR."

ENABLEMENT REJECTION

Claim 21 stands rejected as failing to comply with the enablement requirement under 35 U.S.C. § 112, first paragraph (Ans. 3). The Examiner contends that the Specification "is enabling for a method of introducing the ligand KG-721 into the hydrophobic core of the human HIF2a PAS-B domain and, thereby, changing the surface binding properties of the PAS

domain" (*id.*). However, the Examiner contends that the Specification "does not enable the skilled artisan to affect the surface binding of any HIF2a PAS[-]B domain by 'introducing into the hydrophobic core of the PAS domain . . . [any] foreign ligand" as claimed (*id*).

Findings of Fact (FF)

1. The Specification teaches that foreign ligands may be screened from libraries of synthetic or natural compounds to identify compounds which bind to the PAS B polypeptide domain (Spec. 6: 6-9) using 1H/15N-HSQC NMR.

2. According to the Specification, the polypeptide domain is mixed with a ligand sample and subjected to NMR to determine ligand binding (Spec. 20: 2-16)

3. "Conventional SAR [structure-activity relationship]" can be utilized to derive "ligands of higher affinity and/or specificity" from the lead compound which binds the PAS domain (Spec. 6: 10-11).

4. "This process was specifically exemplified with HIF2a PAS B, wherein a library of 772 compounds (Specification p. 13, lines 6-14) was screened for HIF2a PAS B binding using 1H/15N-HSQC NMR; as seen in Figure 1, 21 hits were obtained for HIF2a PAS B (see also, Specification, p. 18, line 1). From these the inventors developed a 'lead' HIF2a PAS B ligand (Specification, top of p. 31)" (App. Br. 3).

5. "The Specification confirms that the foreign ligands bind the hydrophobic core of HIF-2 PAS B, and as a result, alter the functional surface binding specificity of the PAS domain, wherein the binding specificity is an intramolecular binding affinity of the PAS domain detected

as a change in chemical shifts detected by 1H/15N-HSQC NMR)" (App. Br. 3; *see* Spec. 18: 21-26).

Analysis

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Wright*, 999 F.2d at 1562. In this case, the Examiner contends that scope of claim 21 is not commensurate with the enablement provide by the written description. The Examiner finds the following deficiencies in the Specification:

1) Lacks adequate guidance to "teach the skilled artisan how to direct, restrict, or control binding of any ligand to the hydrophobic core of any PAS domain" (Ans. 4);

2) Does not provide guidance as to the regions of the lead ligand's structure that may be modified without affecting its ability to bind to the hydrophobic core (Ans. 4-5; 10).

> [I]in order for the skilled artisan to practice the elected invention, the specification must provide guidance as to (i) which foreign ligands are likely to bind to the hydrophobic core of any HIF2a PAS-B domain simply by contacting the ligand with the PAS-B domain, (ii) the relationship between structural characteristics of any ligand and the desired function, or (iii) which steps and conditions can be successfully used to induce any foreign ligand to bind to the PAS domain hydrophobic core.

(Ans. 11.)

3) While "human HIF2a PAS-B domain is a defined protein . . . [,] Claim 21 is not limited to methods using the human HIF2a PAS-B domain. The recited method encompasses using all naturally occurring HIF2a PAS-B domains, as well as variants thereof" (Ans. 11).

We find that the Examiner has not met the burden of establishing that claim 21 is not enabled for its full scope. The Specification identifies a lead compound which binds to the hydrophobic core of the HIF2a PAS B domain and causes a "resultant change in the [domain's] functional surface binding specificity" as measured by NMR (FF 4, 5). The Specification states that conventional structure-activity relationships can be utilized to produce ligands of "high affinity and/or specificity" from the lead compound (FF 3). The Examiner has not pointed any deficiency in this teaching nor articulated why it would require "undue experimentation" to use conventional SAR to define additional ligand binding compounds having the claimed activity.

With regard to the Examiner's position that it would require undue experimentation to introduce ligands into the hydrophobic core (Ans. 4; *see* 1) above), the Specification teaches that this can be achieved by mixing ligand with the domain (FF 2).

The Examiner further contends that to practice the claimed invention the Specification must describe "the relationship between structural characteristics of any ligand and the desired function: (Ans. 10; *see* deficiency 2) above).

We do not agree. "[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to

characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976)." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

In re Angstadt, 537 F.2d 498 (CCPA 1976), involved a claim to a process of catalytic oxidation of alkylaromatic hydrocarbons utilizing a catalyst having a generic formula. The Board had affirmed a rejection under § 112, first paragraph, for not providing an enabling disclosure. The dispute centered on the breadth of the catalyst and whether the Specification provided a sufficient number of examples to enable the full scope of the claimed process. "Claim 27 literally reads on thousands of metal salt complexes in which the metal salt moiety may comprise any one of at least 50 metal cations combined with any inorganic anion." *Angstadt*, 537 F.2d at 502, fn.2. The Specification provided working examples; the examples included catalysts which worked in the claimed process, but also a catalyst which did not. *Angstadt*, 537 F.2d at 502. The court did not require the Specification to describe the structural features which enabled the catalysts to work in the claimed process. Rather, the court found the Specification provided sufficient information to choose other compounds and then routinely "determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not." *Angstadt*, 537 F.2d at 503.

In this case, as in *Angstadt*, we conclude that it is not necessary for the Specification to describe the relationship between the structure of the compound and its function to bind to the PAS B domain in order to meet the enablement requirement. The disclosure of a lead compound provides a starting point, and with the conventional principles of SAR, persons of

ordinary skill in the art could routinely produce other compounds and determine their efficacy in the claimed method.

The Examiner also questions of the breadth of the claimed "HIF2a PAS B domain" (Ans. 11; *see* deficiency 3) above). However, as indicated in Ema (*see, e.g.*, Fig. 1 showing conserved regions) and in the Specification (Spec. 1-2), PAS domains, in including PAS B, were well-known in the art at the time the application was filed. Thus, we do not agree that it would require undue experimentation to utilize PAS B domains, other than the human PAS B domain.

Accordingly, we reverse the rejection of claim 21 for lack of enablement.

WRITTEN DESCRIPTION REJECTION

Claim 21 stands rejected as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph (Ans. 3).

The Examiner contends that the Specification only discloses one species within the scope of the claim (Ans. 5).

> [T]he specification fails to describe any other representative species of methods by any identifying characteristics or properties other than the functionality of introducing . . . a foreign ligand into the hydrophobic core of any HIF2a PAS-B domain and, thus, affecting the surface binding properties. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Appellants were in possession of the claimed invention.

(Ans. 6.)

Appellants contend that the "practitioner does not require any a priori structural characteristics of the recited 'foreign ligand' to practice the

[claimed] method. As demonstrated, the method is typically practiced using a library of compounds which need not be structurally characterized" (App Br. 5).

The Examiner has the better argument. The method of instant claim 21 requires "introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain" and then "detecting a resultant change in the functional surface binding specificity of the PAS domain." Thus, the method requires the use of a ligand for it to be carried out. The Specification describes only one ligand that meets the process limitations when contacted with the PAS B domain (FF 4). However, the claims include not only this ligand, but a genus of ligands that change the functional surface binding specificity of the PAS domains. The Specification does not define the genus, other than by function, nor does the Specification describe the structural features of the genus that are necessary for a species of it to bind to the PAS B domain.

A fully described genus must allow one skilled in the art to "visualize or recognize the identity of the members of the genus" and to "distinguish the claimed genus from others." *University of California v. Eli Lilly & Co.* ("*Lilly*"), 119 F.3d 1559, 1568 (Fed. Cir. 1997). Since such a description is lacking in this case, we agree with the Examiner that the claims do not meet the written description requirement.

Appellants appear to argue that this requirement does not need to be met for a method claim (App. Br. 5). We do not agree. In *University of Rochester v. G.D. Searle*, 358 F.3d 916, 926 (Fed. Cir. 2004), Rochester had attempted to Rochester to distinguish *Lilly* and other cases "by suggesting that the holdings in those cases were limited to composition of matter

claims, whereas the '850 patent is directed to a method." The court was not convinced:

> We agree with the district court that is "a semantic distinction without a difference." *Univ. of Rochester*, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, "[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment." *Id.*

Rochester, 358 F. 2d at 926.

For the foregoing reason, we affirm the rejection of claim 21 for lack of written description.

Obviousness rejection

Claim 21 stands rejected over Vogtherr or Amezcua in view of Ema and Fukunaga (Ans. 6).

Findings of Fact

Scope and content of the prior art

6. Vogtherr describes 1H/15N-HSQR NMR to detect ligand binding to proteins (Ans. 6).

7. Amezcua describes the use of 1H/15N-HSQR NMR to detect ligand binding to the PAS domain of PAS kinase (Ans. 6).

Difference between the prior art and the claimed invention

8. Neither Vogtherr nor Amezcua teach 1H/15N-HSQR NMR to detect ligand binding to the HIF2a PAS B domain as recited in claim 21 (Ans. 6).

Reason to combine the prior art

9. Ema teaches that HIF2a ("HLF") regulates transcription by binding to the Arnt DNA binding protein (Ema, *see* Fig. 3; Ans. 6-7).

10. Fukunaga teaches that the aryl hydrocarbon receptor (Ahr), which contains a PAS B domain as does HIF2a, regulates transcription by dimerizing (binding) to Arnt (Fukunaga, at 29270 (Abstract) and 29273, Table 1; Ans. 6-7).

11. Ahr's PAS B domain binds to organic carcinogens, which is a foreign ligand (Fukunaga, at 29270 (Abstract) and 29272, col. 1-2; Ans. 7).

12. Both HIF2a and Ahr have PAS B domains and dimerize with Arnt (FF 9, 10).

13. Based on the structural and functional similarities between HIF2a and Ahr (particular the ability of Ahr to bind foreign ligands; *see* FF 11), persons of ordinary skill in the art would have reasonably expected HIF2a to bind ligands at its PAS B domain (Ans. 7).

14. This expectation is supported by the prior art – Taylor and Cusanovich – who teach that it was known that PAS domains bind ligands to their hydrophobic core (Ans. 16).

15. "In order to identify modulators of the cell's response to hypoxia, one would be motivated to use the method of . . . [Vogtherr or Amezcua] to detect binding of compounds to the HIF2a [which is a hypoxia-sensitive mediator] PAS-B domain hydrophobic core. Motivation to do so derives from the desire to identify activators, inhibitors, and modulators of the cell's response to hypoxia, which would have use in the treatment of cardiovascular diseases" (Ans. 7).

16. "The expectation of success is high, as methods using $^{1}H/^{15}N$-HSQC NMR to detect binding of ligands to proteins, including PAS domains, were known in the art" (Ans. 7).

17. Thus, persons of ordinary skill in the art would have had reason to apply Vogtherr's or Amezcua's method to have produced the claimed method of detecting binding to the HIF2a PAS B domain "as a change in chemical shifts" as determined "by 1H/15N-HSQC NMR."

Analysis

"During examination, the examiner bears the initial burden of establishing a *prima facie* case of obviousness." *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005). In making an obviousness determination, a reason must be provided as to why persons of ordinary skill in the art would have combined the prior art to have arrived at the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

After reviewing the scope and content of the prior art and the reason for combining it, it is our opinion that prima facie obviousness of the subject matter of claim 21 has been established.

The difference between the claimed invention and the prior art is that claim 21 is directed to detecting binding to the PAS B domain of HIF2a, while the prior art uses another PAS domain containing protein (FF 7, 8). The Examiner provides a reason, however, why persons of ordinary skill in the art would have been "motivated" to apply the prior art teachings to HIF2a (FF 15) and evidence that there would have been a reasonable expectation of success of doing so (FF 14, 16). We agree with the Examiner's findings and reasoning, and thus turn to Appellants' rebuttal evidence and arguments.

Appellants argue that "one skilled in the art at the time of our filing would not have expected HIF2a PAS to provide a core for sensory ligand binding" (App. Br. 6). In other words they challenge the Examiner's finding (FF 13, 14, 16) that persons of ordinary skill in the art would have reasonably expected the PAS B domain of HIF2a to have a "hydrophobic core" into a ligand could be introduced as required by claim 21. In support of this position, Appellants contend:

1) "HIF was know to be regulated in several ways by oxygen availability, but only via mechanisms that are based on oxygen-sensitive enzymes that covalently modify portions of the HIFa subunit at sites distant to the PAS domains (Expert Declaration under 37 [ ] CFR [ ]1.132, attached below, and citations therein). These prior findings taught away from any expectation that the HIF PAS domains would be sensory" (App. Br. 6);

2) "HIF2a PASB presents a well-folded domain lacking the dynamic regions of PASK PAS A (Amezucua et al., 2002, p. 1352, col. 1, lines 10-12) and long insertion loops of NPAS2 PAS A (Erbel et al., 2003, PNAS 100, 15504-9), further removing any expectation of core ligand binding" (*id.*); and

3) the "uncontroverted evidence in the form of an expert Declaration" (*id*).

Appellants conclude "that there is no suggestion anywhere that HIF2a PAS would or could provide a receptor for small organic molecules, and no one skilled in the art would try to impose on HIF2a PASB an inference drawn from a functionally and structurally distinct protein like HPASK PAS A" (App. Br. 6).

This evidence is not persuasive. The Examiner acknowledged that non-PAS domains can regulate the response of HIF2a to oxygen, but points out that this evidence does not exclude the HIF2a PAS B domain from also having the ability to bind ligands (Ans. 16.) In support of the position that persons of skill in the art would have reasonably expected HIF2a PAS B to have ligand binding capacity, the Examiner cites the similarities between HIF2a and Ahr (FF 9-14), and cites two publications by Taylor and Cusanovich, respectively, which teach that PAS domains were known to bind ligands (FF 14). Thus, the Examiner did not base the obviousness conclusion on "HPASK PAS A" as Appellants contend (*see* App. Br. 6), but rather on the ligand-binding properties of Ahr and other PAS domain containing proteins.

Appellants have not challenged the evidence provided by the Examiner that other PAS domains were known to bind ligands to their hydrophobic core (FF 14). Nor do Appellants address the Taylor and Cusanovich publications cited by the Examiner (FF 14) to support this conclusion. Furthermore, Appellants do not rebut the Examiner's reasoning, nor the facts upon which it is based, that the similarity between the HIF2a and Ahr proteins would have led persons of ordinary skill in the art to reasonably expect HIF2a to bind ligands at its PAS B domain.

A Declaration under 37 C.F.R. § 1.132 by Dr. Stephen R. Sprang ("Sprang Dec.") is provided by Appellants to support the non-obviousness of the claimed invention. In the Declaration, Dr. Sprang states that "HIF2α PASB presents a well-folded domain, which significantly contrasts with the dynamic regions of PASK PAS A . . . , further removing any expectation of core ligand binding" (Sprang Dec. 2). Dr. Sprang's statement about the

PAS-B domain appears to be based on an "Erbel" reference published in December 2003, which the Examiner states was published *after* the application filing date (Ans. 15). As the instant application appears to have been filed Oct. 1, 2003, the Examiner's conclusion is correct. Appellants have not challenged these facts.

Obviousness is determined "at the time the invention was made." 35 U.S.C. § 103(a) (2004). It is well settled that post-filing date publications, which add to the knowledge of the art, cannot be used to supplement appellants' earlier-filed disclosure. *In re Glass*, 492 F.2d 1228, 1232 (CCPA 1974). There is no evidence that the information in Erbel, published after the application filing date, would have been available to persons of ordinary skill when the invention was made. Thus, we do not consider Erbel as evidence of non-obviousness. Moreover, because Dr. Sprang's opinion is based on part on Erbel, we are not persuaded that there would have been no "expectation of core ligand binding" by the HIF2a PAS B domain.

"[T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In this case, after considering all the evidence of record, we conclude that the Examiner's position is supported by the preponderance of the evidence. Consequently, we affirm the rejection of claim 21.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

lp

RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMENTE CA 92672